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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/614,678	07/07/2003	Alexander D. Romaschin	1148-1-002 CIPF	7389

23565 7590 06/25/2008

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EXAMINER	
DUFFY, PATRICIA ANN	

ART UNIT	PAPER NUMBER
1645	

MAIL DATE	DELIVERY MODE
06/25/2008	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/614,678	ROMASCHIN ET AL.	
	Examiner	Art Unit	
	Patricia A. Duffy	1645	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *28 March 2008*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-20* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-20* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

Continued Examination Under 37 CFR 1.114

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 3-28-08 has been entered.

Claims 1-20 are pending and under examination.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1-7 stand rejected under 35 USC 103(a) as being unpatentable over DeBaetselier et al (US Patent NO> 4,737,455) in view of Winkelhake et al (Journal of Infectious Diseases, Vol. 165:26-33, 1992) for all reasons of record.

Applicants' arguments have been carefully considered but are not persuasive. Applicants argue that DeBaetselier et al does not teach "wherein the amount of oxidant produced is proportional to the amount of analyte present in the sample. DeBaetselier et al specifically teach that light emission is dependent on the dosage providing for both qualitative and quantitative determination of analytes in biological fluids (see column 13, Example 2, 4 and 7). The amount of light produced is therefore necessarily proportional to the amount of oxidant and analyte, otherwise a quantitative determination cannot be made. The claims of the '455 patent specifically provide for measuring the presence and proportion of the analyte (see claims 17-24). Applicants argue that no standard cure relating direct assay readout to analyte level is employed by the art. This is not persuasive, because the claims do not require a standard assay to be performed. The claims merely recite "an amount" and this is interpreted as any amount and therefore reads on detecting the presence or absence of the analyte in a biological sample. Applicants argue that the methods do not require the addition of hybrid cells of DeBaestelier et al. Applicants argue that the claimed invention does not require the addition of the hybrid cells of the patent, yet conversely indicate that the claims encompass such hybrid cells. This is not persuasive, again because the combination substitutes the cells of Winkelhake et al for the hybrid cells of the '455 patent. Therefore, Applicants are arguing the references individually and not as specifically combined. Applicants argue that the source of the white blood cells may include any combination of those endogenously present in the sample. It is noted that the independent claim is not so limited. Applicants are reminded that the claim language is open and thus can provide for additional steps and reagents to perform the quantitation. Applicants argued that DeBaetselier et al do not measure oxidants. This is not persuasive;

DeBaetselier et al teach that chemiluminescence is probably linked to the formation of unstable oxygen compounds such as superoxides, anions, atomic oxygen and hydrogen peroxide (see column 1, third paragraph; the instant oxidant). Applicants argue that Winkelhake et al does not cure the deficiencies of DeBaetselier et al because DeBaetselier et al does not provide the same inventive concept and that the method is novel and unobvious over the art because of the manner in which such detection is performed. This is not persuasive, the arguments with respect to DeBatselier et al were not persuasive and as such the rejection is maintained, because it is obvious to substitute any analyte(antigen)/antibody pair in the assay as modified.

Claims 1, 2, 5, 6, 8, 9, 12, 14, 15, 18 and 20 stand rejected under 35 U.S.C. 103(a) as being unpatentable over Lilius et al (Journal of Bioluminescence and Chemiluminescence, 7:117-122, 1992) for all the reasons made of record.

Lilius et al teach a chemiluminescent assay wherein antigen-antibody complexes as well as the capacity of complement to bind these complexes, can be conveniently and rapidly detected in a simple homogenous assay system by using leukocytes as immunosensors without labeling any of the compounds (page 121, column 1, last full paragraph). Lilius et al teach a quantitative non-labeled immunoassay wherein the recognition of antigen-antibody complexes by the Fc-receptors of phagocytic leukocytes and the subsequent activation of the cells. Lilius et al teach activation is proportional to the amount of immune complexes present can be detected by measuring the intensity of chemiluminescence emitted by the activated cells. In addition to the determinations of antigen and an antibody, the binding capacity of complement can be estimated (see page 117, abstract). Lilius et al teach the measurement of the amount of anti-PPase antibodies or the amount of Ppase (i.e. antigen) in a sample using unfractionated leukocytes. The assay involves combining in a single homogenous assay, unfractionated leukocytes, the antibodies in serum containing complement, and the antigen in 500 ul of Hanks balanced

salt solution, luminal, gelatin and varying amounts of antigen and antibody (Figure 1, page 119) . Lilius et al teach standard curves (see page 118, column 2) for quantitation of antigen or antibody. Lilius et al teach that the amount of antigen can be measured in the presence or absence of complement and if complement was present in the assay, an increased assay sensitivity was present. Lilius et al teach that there was no qualitative difference in the assay when either unfractionated or isolated polymorphonuclear or mononuclear leukocytes were used. Lilius et al differ by teaching the presence of the antibody in serum by adding the antigen (i.e. the instant analyte).

It would have been *prima facie* obvious to one having ordinary skill in the art at the time that the invention was made to alternatively detect the antigen (i.e. the instant analyte) in a sample of a body fluid such as serum by contacting with the cognate antibody because Lilius et al specifically teach that the amount of antigen can be measured.

Applicants argue that there is no reasonable expectation of success for analyte detection by contacting the cognate antibody and that a motivation to make the change and a reasonable expectation of success are required for a rejection under 103 to be proper. With respect to motivation, the courts have held "In contrast to the characterization of some commentators, the suggestion test is not a rigid categorical rule. The motivation need not be found in the references sought to be combined, but may be found in any number of sources, including common knowledge, the prior art as a whole, or the nature of the problem itself. *In re Dembiczak*, 175 F.3d 994, 999 (Fed. Cir. 1999). As we explained in *Motorola, Inc. v. Interdigital Tech. Corp.*, 121 F.3d 1461, 1472 (Fed. Cir. 1997), " there is no requirement that the prior art contain an express suggestion to combine known elements to achieve the claimed invention. Rather, the suggestion to combine may come from the prior art, as filtered through the knowledge of one skilled in the art." *DyStar Textilfarben GmbH & Co. Deutschland KG v. C.H. Patrick Co.*, 80 USPQ2d 1641 (Fed. Cir. 2006). Additionally, motivation was provided. With respect to a reasonable expectation of success, the use of antibodies to detect cognate antigen has

been in the art for more than 20 years. There are textbooks that provide for the requisite assays and conditions. There is nothing beyond routine ingenuity to provide for conditions allowing the interaction of antigen and its cognate antibody. As such, Applicants arguments are not persuasive. It is obvious to the skilled artisan when having an antigen and antibody cognate pair, that the antigen can be used to detect the antibody and the antibody can be used to detect the antigen. This interaction is a fundamental principle established repeatedly in more than 20 years of immunodiagnostic assays. Therefore, Applicants assertion of no reasonable expectation of success is not persuasive.

Applicants also argue that the new limitation is not present in the reference. Lilius et al teach activation as measured by chemiluminescence is proportional to the amount of immune complexes present (i.e. analyte/antibody formed complex of the step a) can be detected by measuring the intensity of chemiluminescence emitted by the activated cells. The amount of light produced is therefore necessarily proportional to the amount of activation oxidant and analyte, otherwise a quantitative determination cannot be made as asserted by Lilius et al. It is noted that Applicants own specification teaches the chemiluminescence assay as a measure of white blood cell activation/oxidant.

Claims 1-20 are rejected under 35 U.S.C. 103(a) as being unpatentable over Lilius et al (Journal of Bioluminescence and Chemiluminescence, 7:117-122, 1992) in view of Winkelhake et al (The Journal of Infectious Diseases, 165:26-33, 1992).

The teachings of Lilius et al are set forth supra. The teachings over Lilius et al as combined supra differ by not assaying for an analyte that is indicative of sepsis in blood.

Winkelhake et al teach glycolipid A is an antigen (i.e. the instant analyte) present in blood in animal models of endotoxemia (i.e. the instant sepsis; page 26, columns 1-2). Winkelhake et al teach monoclonal antibodies that bind pathogenic microorganisms and glycolipid A. Winkelhake et al teach a homogenous chemiluminescent assay wherein the monoclonal antibodies were added to bacteria, incubated to form an opsonic mixture and

then combined with a cell/detection mixture comprising unfractionated diluted whole blood containing leukocytes and luminal buffer. Chemiluminescence was detected by adding the opsonic mixture to the cell/detection mixture.

It would have been *prima facie* obvious to one having ordinary skill in the art at the time that the invention was made to modify the homogenous chemiluminescent assay of Lilius et al as set forth supra, to assay a body fluid for the sepsis glycolipid A analyte (i.e. antigen) of Winkelhake, using the monoclonal antibodies of Winkelhake et al because Lilius et al teach that the homogenous assay is useful for measuring antigen or antibodies and Winkelhake et al teach that glycolipid A is an important indicator of sepsis. As to claims 3, 4, 10, 11, 16 and 17, it would also have been *prima facie* obvious to one having ordinary skill in the art at the time that the invention was made to modify the assay as modified above to use a whole blood sample comprising both analyte and leukocytes in the chemiluminescent assay as combined directly above, because Winkelhake et al teach that whole blood leukocytes are functional in a luminal-dependent chemiluminescence assay and the use of the leukocytes from a sample of whole blood would reduce the number of steps required to perform the assay, Lilius et al teach that the assay is homogeneous and does not require separation of agents. One would have been motivated to use whole blood as both the origin of the leukocytes and analyte for the assay as combined because it would result in a reduced number of assay steps, simplifying the assay and storage of multiple reagents.

Applicants also argue that the new limitation is not present in the reference. Lilius et al teach activation as measured by chemiluminescence is proportional to the amount of immune complexes present (i.e. analyte/antibody formed complex of the step a) can be detected by measuring the intensity of chemiluminescence emitted by the activated cells. The amount of light produced is therefore necessarily proportional to the amount of activation oxidant and analyte, otherwise a quantitative determination cannot be made as

asserted by Lilius et al. It is noted that Applicants own specification teaches the chemiluminescence assay as a measure of white blood cell activation/oxidant.

New Rejections

Claims 8-20 stand rejected under 35 USC 103(a) as being unpatentable over DeBaetselier et al (US Patent NO. 4,737,455) and Winkelhake et al (Journal of Infectious Diseases, Vol. 165:26-33, 1992) as applied to claims 1-7 above, and further in view of Harlow (Monoclonal Antibodies, A Laboratory Manual, Cold Spring Harbor Laboratory, 1988 page 573).

The combination of DeBaetselier et al (US Patent NO. 4,737,455) and Winkelhake et al (Journal of Infectious Diseases, Vol. 165:26-33, 1992) is set forth in the Office actions of 2-21-06 and 1-28-04. The combination differs by not explicitly indicating an antigen standard curve to quantitate an absolute amount of antigen/analyte.

Harlow et al teach that it is conventional in the art to use known amounts of a pure antigen/analyte in a standard curve to determine absolute amounts of antigen/analyte (page 573).

It would have been prima facie obvious to one having ordinary skill in the art to further modify the assay as combined to separately employ pure antigen (i.e. the instant analyte) in a standard curve in order to quantitate the absolute amount of antigen/analyte present in a sample. The skilled artisan would have been routinely aware in order to quantitate an analyte that a standard curve would be required and the assay as combined teaches that it would be useful for quantitation.

Status of the Claims

Claims 1-20 stand rejected.

Conclusion

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Patricia A. Duffy whose telephone number is 571-272-0855. The examiner can normally be reached on M-Th 6:30 am - 6:00 pm. If attempts to reach the examiner by telephone are unsuccessful, the examiner's Supervisor Shanon Foley can be reached on 571-272-0898.

The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

/Patricia A. Duffy/
Patricia A. Duffy, Ph.D.
Primary Examiner
Art Unit 1645